Multi-center (mono-vendor) longitudinal conventional and quantitative spinal cord MRI in Multiple Sclerosis at 3 Tesla - The EMISEP Study: First results

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To cite this version:


HAL Id: inserm-01994583
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Submitted on 25 Jan 2019

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Multi-center (mono-vendor) longitudinal conventional and quantitative spinal cord MRI in Multiple Sclerosis at 3 Tesla

Funding: French Ministry of Health 2012
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Multiple sclerosis (MS) is an often disabling disease of the central nervous system affecting the brain and the spinal cord.

Especially, walking impairment is considered by the patients as the main cause of disability (Hobart et al., 2003).

However, there is a huge heterogeneity in disability progression between patients.

There is a need to identify prognostic factors at the individual level to guide therapeutic decisions.

« Clinico-Radiological paradox »

Barkhof et al. 1999
> 75% of spinal cord images show lesions, more frequently in the cervical than thoracic cord (Ikuta et al. 1976, Nijeholt et al. 1998, Bot et al. 2002, Eden et al. 2018)

Can spinal cord involvement more directly explain motor and sensory impairment and predict disease evolution?
Correlation with impairment

– **Weak**: Focal lesions (Kidd et al. 1993, Nijeholt et al. 1998)
– **Stronger** with quantitative imaging
  • Atrophy (Daams et al. 2014, Kearney et al. 2014)
  • Diffusion and MT imaging (Zackowski et al. 2009, Oh et al. 2013)

Prognosis

– Spinal cord focal lesions have an impact on patient prognosis (Brownlee et al. 2016, Arrambide et al. 2018)
– No long term quantitative studies

Relies on improved image quality for lesion and quantitative imaging (Wheeler-Kingshott 2014, Stroman 2014)
MRI and Multiple Sclerosis – Study design

EMISEP

Funding: Ministry of Health 2012
Led by Rennes Clinical Trials NCT021173375)
PI: Pr. Gilles Edan / Dr. Anne Kerbrat
80 patients - 5-year Brain and Spinal Cord MRI and clinical follow up
3T Research MR scanners

13 centers initially
3 scanner change
<1 inclusion (2 GE scanners)
→ 7 centers included patients
5 Siemens, 1 Philips scanner

+ Healthy controls – M0 and M24
**MRI and Multiple Sclerosis – What about Spinal Cord MRI?**

**EMISEP**

**Inclusion criteria**
- RRMS (MacDonald 2010)
  - First symptoms < 1 year
  - Brain T2 > 9 and/or SC lesion
  - EDSS < 3
  - 18 - 45 years old

**Clinical follow up**
- EDSS, 6min, 8 meter, 9 holes peg test
- Auto questionnaires MSWS12, Qualiveen
- Quantitative: Strength and vibration

**Imaging protocol**
- **Whole cord**
  - Sag T2 TSE and PSIR TSE
- **Cervical cord**
  - Axial 2D T2* ME GRE C1-C3 and C4-C7 → lesion
  - Sag 3D T1 → atrophy
  - Ax 3D GRE with and without MT → MTR
  - Sag 30 dir Diffusion
- **Brain (OFSEP French MS Cohort protocol)**
  - Sag 3D T1 pre Gd
  - Sag 3D FLAIR
  - Ax DP/T2 or 3D T2
  - Ax 30 Dir Diffusion
  - Sag 3D T1 post Gd
81 patients were included between 2014 and 2017
46 healthy controls
to date >18 months follow-up
MRI and Multiple Sclerosis – First results

Magnetization Transfer Ratio

Healthy Controls reproductibility study
  Intra-subject
  Between-subject
  Between-scanner

Patient study at M0

Diffusion imaging

Distortion correction (Snoussi, ISBI 2019)
Lesion location (Chouteau, ECTRIMS 2018)

Lesion imaging

PSIR vs T2 TSE (Rojat et al, JFR 2018)
Measurement of Magnetization Transfer Ratio (MTR) from Cervical Spinal Cord: Multicenter Reproducibility and Variability

Combes, Monteau, JMRI 2018
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

<table>
<thead>
<tr>
<th></th>
<th>IRM 1 (Siemens Verio)</th>
<th>IRM 2 (Siemens Verio)</th>
<th>IRM 3 (Siemens Verio)</th>
<th>IRM 4 (Siemens Skyra)</th>
<th>IRM 5 (Siemens Prisma)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td># subjects</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td># scans</td>
<td>4</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>30</td>
<td>64</td>
</tr>
</tbody>
</table>
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

Imaging details
3D GRE, 52 3mm slabs, 0.7mmx0.7mm in-plane resolution, TR/TE=38/3.57ms, 23°, water excitation and GRAPPA 2
MT0 : no prepulse
MT1 : with vendor MT prepulse (Gaussian, 1200Hz off-resonance)

Processing (Benoît Combès, Post-Doc)
Registration of MT1 to MT0 using the Anima toolbox (v2.3)*
MTR map computation
Whole cord segmentation
Vertebra labeling
Atlas registration
GW/WM segmentation (>0.8)

Spinal Cord toolbox (v3.0)**

*https://github.com/Inria-Visages/Anima-Public/wiki/, ** De Leener, Neuroimage 2017
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

Overall multi-scanner variability

Between-scanner variability

Between-session variability (same participant, same scanner)

Between-participant variability

Inter-scanner variability (different scanners, same participant)

Inter-participant variability (different participants, same scanner)

Investigated variability

Measured variability
MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability

Inhomogeneous MTR values along the cord (C4-C6 plateau)

Between-scanner and between-subject variability overlap
Inhomogeneous MTR values along the cord overlap intercenter (scanner) and intersubject variability.
**MTR from Cervical Spinal Cord: Multicenter Reproducibility and Variability**

**Variation coefficient** = \( \frac{\text{standard deviation}}{\text{mean}} \times 100 \)
Global variation coefficient of 3% (0.9 pu) is compatible with the detection of 1pu MTR Variations between 2 groups (45 per group, type I error= 0.05 and type II error= 0.10)

These results show that it is possible to use cervical cord MTR in multicenter studies

Yet

This was evaluated on a single vendor
Inhomogenous MTR along the cord
The investigation in longitudinal studies remains challenging
Focal and diffuse cervical spinal cord damage in patients with early relapsing-remitting MS: A multicentre magnetization transfer ratio study

Combes, Kerbrat, Multiple Sclerosis Journal 2018
Goals

Quantify MTR changes in early RRMS patients in comparison with healthy controls
Describe spatial distribution within and outside lesions
Correlate MTR measurements with clinical scores
MRI and Multiple Sclerosis – First results

MTR from Cervical Spinal Cord: Patient vs Controls at M0

Participants
- 60 RRMS patients
- 34 controls

Five 3T scanners (same manufacturer)

MRI acquisition
- Lesion imaging (patients)
  - Sag PSIR
  - Sag T2
  - Axial T2*
- MT imaging
  - MT1
  - MT0
- Morphological imaging
  - 3DT1

Image processing
- Lesion mask
- MTR maps
- SC segmentation and vertebral labelling

Results
- T2 lesion load
- Lesion MTR
- Normal appearing SC MTR
- Whole SC MTR
- Mean cross-sectional area

Mean value for:
- C4-C6 (most reproducible levels)
- Cl, l=1,…,7
- At different distances from cord periphery and barycentre
MTR from Cervical Spinal Cord: Patient vs Controls at M0

MTR (C4-C6) is significantly lower in patients versus controls considering the normal appearing spinal cord (lesion excluded) and the whole spine.
MRI and Multiple Sclerosis – First results

The more focal lesions the lower the MTR, also in the normal appearing spinal cord

no lesion

1-2 lesions

3 lesions or more
MTR from Cervical Spinal Cord: Patient vs Controls at M0

In the sagittal plane

A

B

C

Patient-to-control MTR difference (pu)

Vertebral level

Mean lesion fraction

C1 C2 C3 C4 C5 C6 C7

NASC

WC
MTR from Cervical Spinal Cord: Patient vs Controls at M0

In the axial plane

(Pardini et al. 2016)
### Correlation with clinical scores

<table>
<thead>
<tr>
<th></th>
<th>EDSS</th>
<th>Pyramidal EDSS</th>
<th>8m</th>
<th>6 minutes</th>
<th>12 MSWS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MTR</strong></td>
<td>-0.21 (p = 0.14)</td>
<td>-0.27 (p = 0.05)</td>
<td>-0.08 (p = 0.57)</td>
<td>0.13 (p = 0.36)</td>
<td>-0.12 (p = 0.39)</td>
</tr>
<tr>
<td><strong>Cord Lesion volume</strong></td>
<td>0.26 (p = 0.06)</td>
<td>0.28 (p = 0.03)</td>
<td>0.00 (p = 1.00)</td>
<td>-0.26 (p = 0.05)</td>
<td>0.30 (p = 0.03)</td>
</tr>
<tr>
<td><strong>CSA</strong></td>
<td>0.08 (p = 0.58)</td>
<td>0.01 (p = 0.92)</td>
<td>0.04 (p = 0.75)</td>
<td>-0.04 (p = 0.79)</td>
<td>-0.06 (p = 0.67)</td>
</tr>
<tr>
<td><strong>Brain lesion volume</strong></td>
<td>0.15 (p = 0.27)</td>
<td>0.12 (p = 0.38)</td>
<td>-0.12 (p = 0.37)</td>
<td>-0.11 (p = 0.43)</td>
<td>0.07 (p = 0.63)</td>
</tr>
</tbody>
</table>
Diffuse and focal spinal cord burden can be measured at the beginning of the disease, and is correlated with lesion load.

Longitudinal data needs to be processed to investigate whether initial burden can predict disability at 1, 2, 3 and 5 years.
A particular case
MTR from Cervical Spinal Cord: Longitudinal data

A particular case

<table>
<thead>
<tr>
<th>M0</th>
<th>M12</th>
<th>M24</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="M0" alt="Image" /></td>
<td><img src="M12" alt="Image" /></td>
<td><img src="M24" alt="Image" /></td>
</tr>
</tbody>
</table>
Whole cord MTR change between M12 and M0 in a group of 39 patients

...ongoing work
Acknowledgments

- Gilles Edan, Anne Kerbrat and Benoît Combès
- EMISEP study group: Neurologists, radiologists, MR Techs, MR Physicists, Research assistants from Montpellier, Strasbourg, Marseille, Lyon, Clermont-Ferrand, Nîmes and Rennes (list @ team.irisa.fr/visages/emisep)
- Research group Visages (Empenn) Univ Rennes, CNRS, Inria, Inserm, IRISA UMR 6074, Empenn - ERL U 1228
- Ponnada Narayana, Maria Rocca and Denis Ducreux
- Virginie Callot
- Julien Cohen-Adad and his team